

The University of Chicago

THE EFFECT OF SODIUM IODIDE ON THE CRETIN RABBIT

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE BIOLOGICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY
DECEMBER, 1941

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HOWARD MAUTHE

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The action of inorganic iodine compounds on the mammalian organism derives its interest not only from the obvious importance of this element in the secretion of active hormone by the thyroid gland under physiological conditions, but also from the marked pharmacological action of iodine when it is used to control hyperthyroidism. A high percentage of cases of human hyperthyroidism respond to large doses of iodine or iodides with a marked lowering of the basal metabolic rate and a consequent remission of most of the symptoms. Since it has become possible to produce hyperthyroidism in the laboratory by injection of thyrotropic extracts of the anterior pituitary, a similar remission has been observed in animals when iodine is administered along with the pituitary hormone (1, 2, 3, 4). As Friedgood (2) suggests, there are several possible mechanisms by which this experimental remission might take place: first, the iodine might be inactivating the thyrotropic hormone in the circulating blood; second, the iodine might be acting on the thyroid gland itself in such a way as to prevent the usual increase in formation and release of the thyroid hormone; third, the iodine might inactivate the thyroid hormone in the general circulation; fourth, the iodine might directly depress the rate of oxygen consumption of the individual cells of the body. Of course it is possible that more than one of these mechanisms is operating, and it is conceivable, although not probable, that some entirely different chain of events is responsible.

The experiments to be described were designed to determine whether or not the fourth factor is of importance. None of the experimental evidence at hand gives much valid information on this

point. When inorganic iodine is given to normal animals, the results are extremely variable. Anderson and Evans (4) reported a fall of six per cent in the basal metabolic rate of normal guinea pigs treated with potassium iodide. Webster and Chesney (5) observed a temporary fall in normal rabbits, a rise in goitrous rabbits. Hara (6) and Cordonnier (7) have claimed that no substantial change occurs. Freud (8) found that slow injection of potassium iodide into dogs resulted in increased oxygen consumption. Hildebrandt (9), Liebesny (10), Marine, Deutsch, and Cipra (11), Siebert and Smith (12), and Salvadori (13) all report variable results. Apparently these results are due to the fact that the iodine exerts an influence on the thyroid which varies with the physiological condition of the gland, and as long as such a powerful regulator as the thyroid is present, changes in its rate of activity will far overshadow any effects due to the iodine alone. This view is substantiated by the experiments of Marine, who showed that thyroid glands with different grades of hypertrophy will take up different amounts of iodine when perfused (14). Furthermore, it has been shown beyond question that inorganic forms of iodine have a powerful effect on the histological appearance of the thyroid gland which varies with the condition of this organ (15, 16, 17).

Under such circumstances, the only way to determine the direct effect of inorganic forms of iodine on the tissues is to administer the iodine to a completely thyroidectomized animal. There have been two attempts to perform this experiment, by Siebert (18), and Siebert and Linton (19). These investigators found that both potassium iodide and diiodotyrosine caused a lowering of the basal metabolic rate of thyroidectomized guinea pigs. Siebert concludes that "the peripheral effect of potassium iodide

in causing a depression of the basal metabolic rate is at least partly responsible for the fact that potassium iodide does not increase the basal in the normal animal, although it stimulates the thyroid gland." The further inference of this work is that iodides exert their depressing influence on the basal metabolic rate in hyperthyroidism at least partly through a direct action on the individual cells. These results seem rather strange in the light of two considerations: first, it is now practically unanimously conceded that iodides do not have any appreciable effect upon the rise in basal metabolic rate induced by treatment with thyroid or thyroxin; secondly, Swingle (20) long ago showed that large amounts of inorganic iodine are just as effective as thyroid in promoting the metamorphosis of thyroidectomized amphibian larvae, so that if any effect at all occurred in thyroidectomized mammals one would suspect that the basal metabolic rate would rise. Furthermore, Siebert and Linton themselves call attention to the possibility that their animals might not have been completely thyroidectomized. In view of this fact, and considering the importance the experiment has acquired in the search for the mechanism of iodine remission in hyperthyroidism, it was decided to carry out the experiment on what is believed to be the most completely thyroidectomized animal obtainable, namely, the cretin rabbit.

Animals used.--Cretinism in the rabbit has been described quite thoroughly by Bassinger (21), whose excellent treatment contains references to all the previous work on this topic. The rabbits used in this experiment were obtained by essentially the same technique used by Basinger. They were all raised in the laboratory, since first attempts showed it to be practically impossible to keep alive animals brought in from the outside. The smallest rabbit in each litter was kept as a control; the others were

very carefully thyroidectomized under ether anesthesia at the age of three weeks with the aid of a binocular microscope, and then kept for at least twenty-four weeks before the experiment was begun. By this time the symptoms of cretinism are well developed. The most prominent of these symptoms are: retardation of growth (50-65% of the normal weight when mature); dry and scabby skin; rough, sparse hair; general sluggishness; low metabolic rate; and high serum cholesterol. Muscular and skeletal weakness and susceptibility to infection are also frequently seen. Only rabbits showing all or nearly all of these symptoms were used in this experiment, and the individual symptomatology of these cretin animals is reviewed in Table 1, where their status is compared with that of three normal animals from the same stock. The "questionable cases" in Table 1 are very interesting apropos the question as to whether an animal is "completely" thyroidectomized or not. Basinger reported that in his long series of over 140 operations, he was able to produce cretinism in 86 cases, that is, about 60 per cent of the operations were successful. In this series of animals, I was able to produce cretinism in 16 cases out of 38 operations, or 42 per cent successes. These are remarkably low percentages for an animal like the rabbit, which is reputedly so easy to thyroidectomize. The animals which did not become true cretins showed all degrees of hypothyroidism; the status of seven of these animals is reviewed in Table 1 under "questionable cases." It should be especially noted that, with the exception of number 55, which was completely normal by any standards, all of these animals show depressed basal metabolic rates, elevated serum cholesterol, and even other symptoms. There unquestionably is a marked diminution in thyroid function in these cases, but since true cretinism did not develop, one would hesitate to say that

TABLE 1

SYMPTOMS PRESENT IN THE CRETIN RABBITS COMPARED WITH THE NORMALS
AND SEVERAL ANIMALS OF QUESTIONABLE STATUS

Rabbit No.	Date Thyroid Removed	Maximum Weight (gm.)	Max. Wt. of Litter Mate (gm.)	Ave. BMR (Cal/M ² /Hr)	Ave. Cholesterol (mg%)	Appearance		
						Skin	Hair	Other
CRETINS								
33	9/11/40	1630	2860	19.7	203	Dry, scabby	Thin, gone from rump	Skin sores
40	9/12/40	1700	3250	20.0	156	Dry	Rough, sparse	
41	9/12/40	1500	3250	21.0	127	Dry	Rough, sparse	
42	9/12/40	1560	3250	21.4	219	Dry, scabby	Rough, sparse	
44	9/12/40	1940	3250	21.2	68	Dry, scabby	Thin, gone from rump	
47	11/1/40	1540	2640	21.7	147	Almost normal	Slightly rough	Two abscesses
60	12/15/40	2090	3100	21.9	209	Dry, scabby	Rough, sparse	Fr. legs very weak
61	12/15/40	1500	3100	21.2	225	Dry, scabby	Rough, sparse	Several abscesses
62	12/15/40	1930	3100	19.7	211	Dry	Rough	
63	12/15/40	1820	3100	20.6	242	Dry, scabby	Rough, sparse	Front legs weak
NORMALS								
23		2760		26.2	49	Normal	Smooth, glossy	
51		2640		28.9	45	Normal	Smooth, glossy	
58		2900		30.4	29	Normal	Smooth, glossy	
QUESTIONABLE CASES								
18	7/10/40	2100	2760	20.9	132	Normal	Smooth	Quite active
19	7/10/40	2440	2760	24.5	60	Normal	Smooth	Very active
38	9/12/40	2060	3250	20.2	265	Normal	Smooth, glossy	Quiet and sluggish
39	9/12/40	2660	3250	18.6	124	Dry	Rough, sparse	
54	11/1/40	2600	2900	19.3	40	Normal	Smooth, glossy	Somewhat sluggish
55	11/1/40	2940	2900	29.1	40	Normal	Smooth, glossy	Very active
59	12/15/40	2560	3100	20.9	294	Dry, scabby	Rough, sparse	Numerous abscesses

any of them are completely thyroidectomized. These cases serve to illustrate the point that it is dangerous to consider an animal to be completely thyroidectomized solely on the basis of a careful operation resulting in a low metabolic rate and elevated blood cholesterol.

An interesting sidelight may be mentioned here. Basinger reported that in some litters, the percentage of successful operations was very high, in others very low. This is entirely corroborated by my own experience with this series of animals. There seem to be hereditary differences in the degree of attachment of the gland to the larynx which makes successful operation in some litters more difficult than in others. Of course part of this difference may be due to an inherited tendency toward the possession of accessory thyroid tissue.

Method.--Of the symptoms of hypothyroidism which have been mentioned, there are two which are accessible to more or less accurate measurement. These are the basal metabolic rate and the serum cholesterol. It was therefore planned to follow both of these throughout the experimental period. The basal metabolic rate determinations were made with the common type of apparatus consisting of an oxygen-filled spirometer connected with an animal chamber equipped with a soda-lime absorber. The determinations were carried out in a room where the temperature in both the spirometer and chamber could be kept reasonably constant, the temperature in the animal chamber being kept in the range of 28-31 degrees Centigrade. When placed in the chamber the animal was restricted as to space and watched constantly for activity; any periods of activity were subsequently disregarded in making the calculations. The animals were subjected to a long training period until they would lie quietly in the apparatus, and previous

to every determination were fasted from 18 to 24 hours. The oxygen consumption was converted into calories by the assumption of an R. Q. of .83, and then the heat production expressed in terms of one square meter of surface area. Surface area was determined from the formula

$$S = 10 w^{2/3}$$

where S represents the surface area, and w the weight.

Serum cholesterol was estimated by an adaptation of the method of Leiboff (22), allowing the extraction of the cholesterol from the serum to be carried out in a specially constructed Evelyn colorimeter tube. In Figure 1, the necessary equipment is shown. This equipment consists of a regular Evelyn colorimeter tube from which a section has been removed, and a short (about 3 cm.) length of nine millimeter soft glass tubing fused in, thus producing a constriction on which a calibration mark can easily be placed. The tube must be made in such a manner that the calibration mark will fall midway on the constriction. It is then standardized against all the other tubes in the usual way, and calibrated to hold 14 cubic centimeters. This assures that the undisturbed bottom portion of the tube through which the light beam of the colorimeter passes will hold more than the required 10 cubic centimeters of liquid. Into this tube fits a funnel-shaped glass inset which has a groove traveling its entire length. This groove prevents the inset from shutting off the neck of the tube and allows chloroform vapor to pass freely. In the glass inset a small square of fat-free absorbent paper can be placed. The whole tube then fits onto a reflux condenser in the manner shown. The procedure followed is to draw the blood from an ear vein and centrifuge it down. The serum is then pipetted off the top and exactly

0.2 cc. deposited on the absorbent paper and allowed to dry, the paper, inset, and tube having been already assembled. When the serum is completely dry, about 5 cc. of reagent chloroform is run

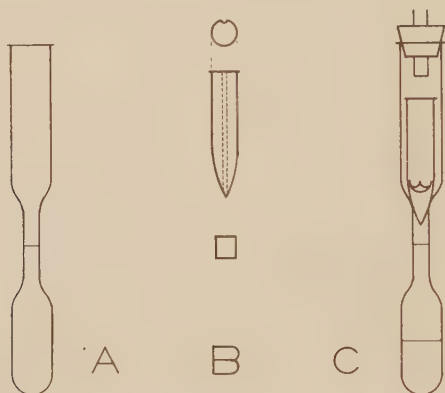


Figure 1.--Apparatus used in cholesterol determinations: A. Modified Evelyn colorimeter tube showing fused-in constriction and calibration mark. B. Above, glass inset which allows vapors to pass freely upward. Below, square of fat-free absorbent paper. C. Apparatus completely assembled and attached to tube of reflux condenser, showing chloroform in lower portion of tube.

into the tube, and the tube placed on the reflux condenser. The bottom portion of the tube is immersed in a glycerine bath which is heated, and the chloroform is allowed to reflux for thirty minutes. The tube is then taken off the condenser, the inset removed, and the tube placed in a water bath at 25° Centigrade. Four cc. of acetic anhydride is then added, and the volume made up to the 14 cc. mark with chloroform, thus giving an original solvent volume of 10 cc. One-tenth cc. of concentrated sulfuric acid is then added, and the tube stoppered and returned to the water bath until maximum color development has taken place. This usually requires about 18 minutes. At the end of this time the outside of the tube is carefully wiped dry and the tube inserted directly

into the Evelyn colorimeter. The reading is taken and the calculation made in the usual way. It may be noted that the only difference between this method and the usual one employed with the Evelyn colorimeter is that Leiboff's chloroform extraction method has been substituted for the laborious alcohol-ether extraction. The saving in working time, however, is considerable.

The experimental procedure followed consisted of three periods of observation. During the first period, the animals' basal metabolic rates were taken on the average of once a week until a more or less definite level was established. The length of this period ranged from 6 to 10 weeks, and the serum cholesterol_s were determined several times during this time. During the second period of approximately one month, the animals were given sodium iodide solution by mouth in doses ranging up to 200 milligrams per day, and the basal metabolic rates and serum cholesterol_s were followed as before. The third period consisted of a number of follow-up observations made after iodide administration was discontinued. Sodium iodide was used in preference to potassium iodide in order to avoid any possible toxic effects due to the potassium ion.

Results and Comment.--The basal metabolic rate curves for the individual animals are shown in Plates I, II, and III. Here the animals' metabolic rates (in calories per square meter per hour) on the ordinates are plotted against time (in days) on the abscissae. In addition to the individual curves, two composite curves are shown, one for the ten cretins studied, and another for the three normals. The range and averages obtained in the basal metabolic rate determinations before, during, and after treatment with sodium iodide are given in Table 2. An examination of the individual curves for the cretin animals reveals that of

the whole group, number 47 is the only one to show a distinct rise, although numbers 33, 60, and 61 also show a detectable elevation. The important thing to be observed is that none of the cretin animals showed any fall in basal metabolic rate. A glance at the figures in Table 2 shows that this is essentially correct. Numbers 47, 60, and 61 showed rises of 18, 11, and 14 per cent respectively, and all the other changes are 7 per cent or less; these smaller changes can scarcely be judged to be significant in any individual case. The only animal whose basal metabolic rate showed any depression at all was number 40, and this was a depression of only 4 per cent. From these data, as well as the composite curve for all cretins shown in Plate II, the general impression is that despite the large doses used and the frequency with

TABLE 2

EFFECT OF SODIUM IODIDE ON THE BASAL METABOLIC RATE
(VALUES GIVEN IN CALORIES PER SQUARE METER PER HOUR)

Rabbit Number	Before Sodium Iodide			During Sodium Iodide			After Sodium Iodide			% Change of ave. with NaI
	Low	High	Mean	Low	High	Mean	Low	High	Mean	
CRETINS										
33	18.1	21.6	19.7	21.4	24.7	23.2	23.0	25.7	24.3	+18
40	17.2	22.0	20.0	18.9	19.7	19.2	19.9	21.7	21.0	-4
41	18.5	23.8	21.0	18.8	23.2	21.3	22.2	24.2	23.1	+1
42	17.9	24.1	21.4	20.3	24.0	21.8	23.8	26.3	25.1	+2
44	18.4	25.9	21.2	19.8	24.2	22.5	23.6	25.2	24.4	+6
47	20.4	23.1	21.7	20.2	27.0	23.2	21.6	23.9	22.8	+7
60	20.2	23.4	21.9	23.5	26.1	24.4	23.0	26.0	24.4	+11
61	19.6	22.8	21.2	22.2	26.7	24.1	22.8	25.5	23.8	+14
62	18.3	20.6	19.7	19.0	21.9	21.3	17.9	19.7	18.6	+3
63	17.6	23.2	20.6	18.7	22.6	20.5	24.0	24.8	24.4	0
Average			20.8			22.1			23.2	+6
NORMALS										
23	25.1	28.0	26.2	30.7	52.2	38.2	31.0	34.4	33.2	+46
51	26.3	31.7	28.9	29.8	35.8	33.8	24.8	27.2	25.9	+13
58	27.8	33.6	30.4	23.6	39.9	31.5	25.3	30.0	28.2	+4
Average			28.5			34.2			29.1	+20

which they were given, the change produced in the basal metabolic rates of the cretin rabbits was a very slight rise; most certainly

no fall in the basal metabolic rate can be seen. We may conclude from this that any depression in basal metabolic rate which occurs in either the normal or the hyperthyroid animal as the result of inorganic iodine administration is almost certainly not due to the action of the iodine on the tissues directly. A further conclusion is that inorganic forms of iodine in and of themselves have little if any calorogenic activity in this species of mammal.

In contrast to these results, the effect on the normal animals studied are striking. All three of these animals show a definite rise, but after about three weeks of sodium iodide administration the basal metabolic rate began to return to normal. In the case of number 58, when the basal metabolic rate started to decrease it reached a level which was below normal for that particular animal. This great variability in the effect on the normal animal is entirely in keeping with the results obtained by other investigators, and is very well brought out by the figures in Table 2.

There remains to be mentioned one observation on the cretin animals, and that is that the average basal metabolic rate for all the cretins was about 5 per cent higher for the third period of the experiment (after sodium iodide was discontinued) than it was during the administration of sodium iodide. The significance of this rise is not entirely understood, but it should be mentioned that right at the time when this rise occurred the weather turned cold and the heat in the animal rooms had not yet been turned on, so that for about two weeks during the third period the animals were subjected to temperatures which were about 10-15 degrees Fahrenheit below those which obtained throughout the remainder of the experiment.

The results obtained from the serum cholesterol determinations are summarized in Table 3. It should be pointed out in the beginning that the cholesterol level in the blood of the thyroid-ectomized animal is very unstable and variable. Because of this one must be careful not to read too much meaning into results obtained from a small number of determinations. From the table it can be seen that 4 of the cretins and 2 of the normal animals

TABLE 3

EFFECT OF SODIUM IODIDE ON THE SERUM CHOLESTEROL
(VALUES GIVEN IN MILLIGRAMS PER 100 MILLILITERS)

Rabbit Number	Before Sodium Iodide			During Sodium Iodide			% Change of Ave. with NaI
	Low	High	Mean	Low	High	Mean	
	CRETINS						
33	173	226	203	231	301	266	+31
40	107	212	156	152	208	174	+12
41	103	169	127	226	242	234	+84
42	153	284	219	204	274	242	+11
44	64	82	68	76	161	118	+74
47	120	213	147	177	204	194	+32
60	169	248	209	197	301	261	+25
61	202	259	225	244	260	251	+12
62	153	237	211	97	121	116	-45
63	164	290	242	155	240	198	-16
Average			181			205	+13
NORMALS							
23	34	76	49	32	86	58	+18
51	37	48	45	36	46	41	-9
58	21	33	29	41	152	96	+231
Average			41			65	+59

showed changes of 18 per cent or less. In my opinion, these changes cannot be considered to be significant. The changes of 25 per cent or more, however, probably represent definite changes in the level of cholesterol in the blood. If this is assumed to be correct, then 5 of the cretin animals (numbers 33, 41, 44, 47, and 60) showed a definite increase in serum cholesterol due to the treatment with sodium iodide, while one cretin (number 62) showed

a decrease. The normal animals showed no significant change except in the case of number 58, where a large increase occurred. This increase exactly coincided with the time when the basal metabolic rate of number 58 was depressed below normal by the sodium iodide. When the experiment was begun it was hoped that the serum cholesterol would mirror the basal metabolic rate, since in hyper- and hypothyroidism these two quantities show a negative correlation with respect to one another. Only in the case of rabbit number 58 did this occur. In the case of the cretins, a rise in serum cholesterol was the predominant effect, and thus it would seem that sodium iodide by itself is capable of altering the serum cholesterol independent of any changes in basal metabolic rate. If this is true, then we might consider the following as an hypothesis: The secretion of the thyroid gland is capable of lowering the serum cholesterol, and if the amount of thyroid secretion present in an animal is reduced, then the serum cholesterol becomes elevated. On the other hand, large doses of sodium iodide seem to have a tendency to make the serum cholesterol rise. If the thyroid gland is present, however, the sodium iodide also influences its output of secretion, so that the effect of the iodide alone is modified by the thyroid changes which the iodide produces.

SUMMARY

The basal metabolic rate and serum cholesterol of 10 cretin rabbits and 3 normal rabbits were studied during the administration of sodium iodide in doses up to 200 milligrams per day for 30 days. The average metabolic rate of the cretins showed only a very slight rise (6 per cent), and in none of these animals was a decrease observed. The metabolic rate of the normal animals showed an increase which was temporary and varied in magnitude; one showed only a small increase followed by a depression below normal.

The serum cholesterol of 5 of the cretin rabbits showed an increase during sodium iodide feeding, 1 showed a decrease, while the others showed no significant change. Two of the normal rabbits had unchanged serum cholesterols, while the third showed an increase at the time when the basal metabolic rate was depressed below normal by the sodium iodide.

It is concluded, (1) that any depression in the basal metabolic rate of either the normal or the hyperthyroid animal which results from the action of inorganic iodine compounds is not due to the action of the iodine on the tissues directly, and (2) that inorganic forms of iodine in and of themselves probably have little if any calorigenic activity in mammals.

A simplified method for the estimation of blood or serum cholesterol is described.

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EXPLANATION OF PLATES I, II, AND III

In the three plates which follow, the individual basal metabolic rate curves are shown for the 10 cretine and the 3 normal animals. Two composite curves are also shown, one for all the cretin animals, and one for the normals. These composite curves were made by superimposing the curves in such a way that the dates on which sodium iodide administration was begun coincided. The heights of the individual curves for every 5 days before and after this date were then averaged and the averages plotted as one curve. In all curves, the ordinates are marked off in calories per square meter per hour, and the abscissae are marked off in days. The amounts of sodium iodide which were given are indicated by the short vertical lines just above the abscissa in each case. Each one of these lines indicates one dose. These lines are of three lengths; the shortest ones indicate a dose of 50 milligrams, the intermediate ones a dose of 100 milligrams, and the longest ones a dose of 200 milligrams. Since the dosage varied somewhat in the individual cases, the period of iodide administration on the composite curves is shown by two arrows.

PLATE I

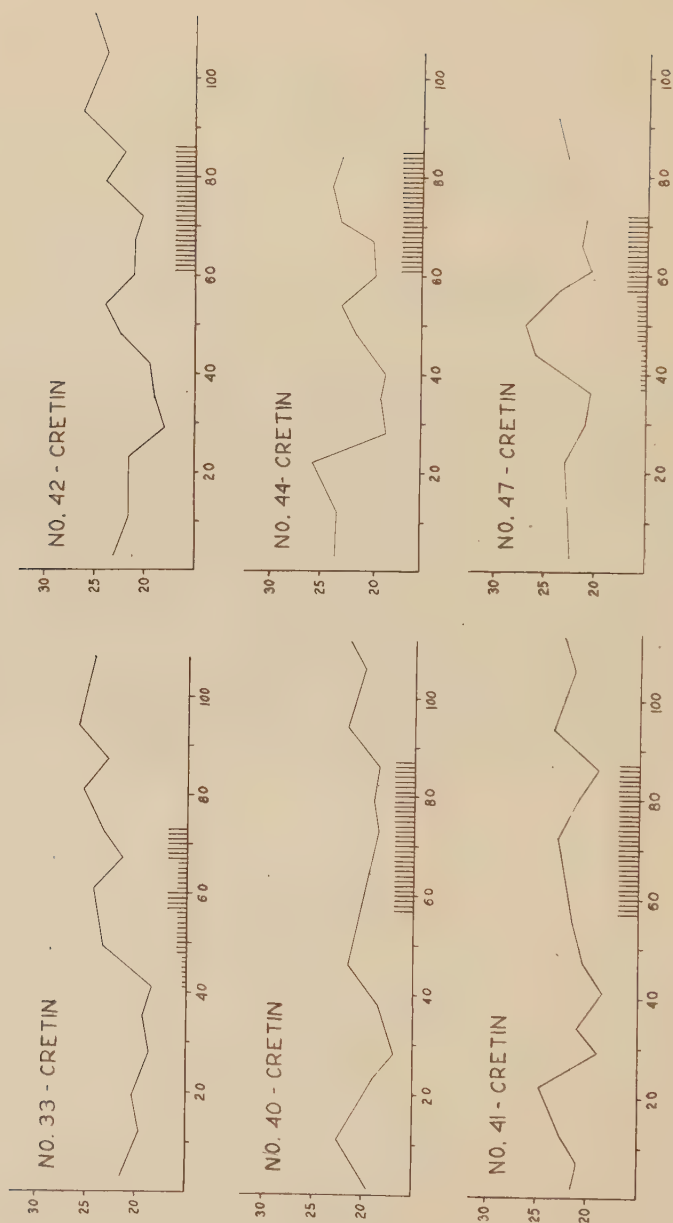


PLATE II

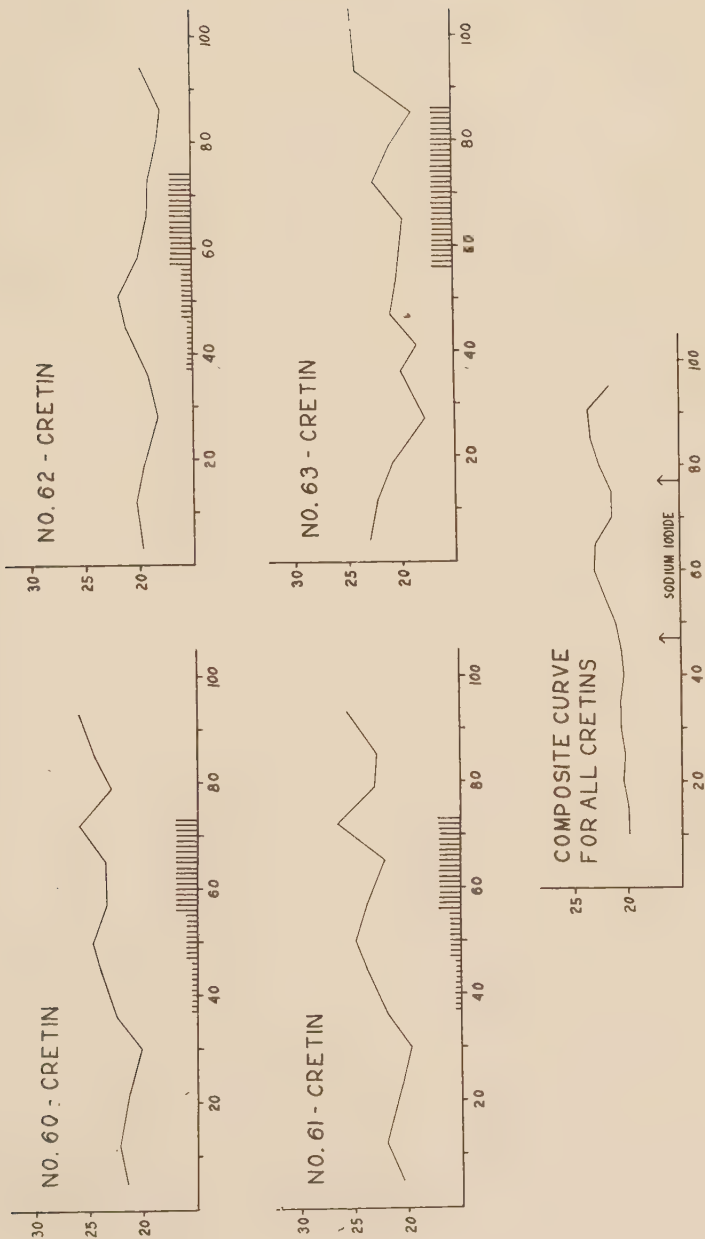


PLATE III

